



COVID-19 in Dermatology

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Disclosures



- None

Objectives



- 1. Identify patterns of skin injury SARS-CoV-2
- 2. Recognize common cutaneous side effects of COVID vaccine
- 3. Review safety and efficacy of COVID vaccine in patients receiving biologic agents for immunosuppression

Patterns of Injury



- Maculopapular (47%)—Pityriasis rosea-like ,follicular, shorter duration
 - Pernio-like (19%)
 - Late onset
 - Vesicular (9%)
 - Concurrent or late in course of disease, monomorphic on trunk, zoster-like
 - Urticarial (19%)
 - Livedo Reticularis (6%)
 - Enanthems
 - Half moon nail
-
- Casas CG et al. Classification of the cutaneous manifestations of COVID 19: a rapid prospective nationwide concensus study in Spain with 375 cases. Br J Dermatol. 2020 Apr 29
 - 5. Jiminez-Cauhe J et al. Enathem in Patients with COVID-19 and Skin Rash. JAMA Dermatol 2020 July 15 2550

Maculopapular Eruption



Maculopapular Eruption –Pityriasis Rosea Like



Erythema Multiforme-Like



Maculopapular



- Mostly present on trunk, \pm pruritus,
- PR like (5.7%), EM like (9.7%) were mostly present in females (88.2%), EED like (2.3%)
- eruptions occur either **simultaneously** with onset or **after** onset of other COVID symptoms
 - Mean length for eruption is 8 days, lasting 7.2 ± 4.3 days
- Exclude drug eruption, other viral exanthems
- Associated with highest rate of hospital admission
- Corresponds to early inflammatory phase (TEI) or secondary infection phase (TSI)
- Spontaneously resolve, Rx with topical/systemic steroids, antihistamine

Vesicular



Vesicular



- commonly abdomen, arm, legs/buttocks, hands, back, and chest
- **Monomorphic** vs polymorphic (zoster)
- Localized (25%) or diffuse (75%), itching (68%), hemorrhagic
- more common in middle-aged patients,
 - Most are symptomatic, pruritus (68-72%) pain (50%)
 - lasted with mean duration of 10.4 days
- most common associated symptoms : cough, fever, asthenia, and sore throat
- The majority of vesicular rashes occur **after** COVID-19 symptoms (29-79.2%) or **concurrently** (12.5-56%) seldom before
 - Corresponds to early inflammatory phase (TEI) and potentially secondary infection phase (TSI)

Urticarial



Urticarial



- Similar pattern to maculopapular
- Itching very common (92%)
- Lasted for shorter period 6.8days, usually appeared *concurrently* with other symptoms, associated with more *severe* disease
 - likely correspond to the viral symptom phase (TS) or early inflammatory phase (TEI)

COVID Toes—Perniosis Like



Pseudo-Chillblains



- erythematous or violaceous papules on acral surfaces feet (94%), hands (15%)
- Edema on several toes
- common in children or young adults otherwise healthy,
 - 50% asymptomatic or with mild symptoms pain/burning (66%), pruritus (43%), cold intolerance (6.9%)
- DDx: post infectious vasculitis, perniosis, coagulopathy, septic emboli
- Most commonly **after** the onset of COVID-19 symptoms (35.8-54%)
- occurring in **late stage (post acute tail phase)** (TT) or convalescent phase of disease
 - not actively infectious, represent secondary inflammatory response
- **negative serology testing**

Cardoro et al Pediatric Dermatology 2020;37:419423

Pseudo-Chillblains



- Outpatient setting—mild
- Workup for COVID if systemic findings—vasculitis, clotting disorder, CTD, and hypercoagulable states (if severe), autoimmunity and cold associated disease
 - COVID Nasal PCR swab, IgG/IgM, CBC with diff, ANA, RF, cold agglutinins, cryo, C3, C4, CH50, CRP, ESR, d-dimer, fibrinogen, antiphospholipid antibodies, anticardiolipin
- Histology: lymphocytic vasculitis
- Treatment
 - Topical steroids ie clobetasol
 - ASA
 - Topical nitroglycerin tacrolimus, minoxidil
 - Nifedipine 20-60mg/day,
 - hydroxychloroquine 5mg/kg/day
 - pentoxifyline,
 - nicotinamide 500mg tid

Q and A Dermatologic changes with COVID 19: What we Know and Don't Know, Dermatology Times June 2020

Livedoid Eruptions





Livedo Reticularis/Vasculitis



- several types, livedo reticularis, livedo racemosa, and retiform purpura
- Suggests occlusive vascular disease
- Retiform purpura progressing to purpura fulminans (gangrene acral sites)
- More **severe disease** in elderly, ICU patients with high mortality
 - DIC (elevated d-dimer, CRP, fibrinogen products)
 - All patients are anticoagulated
- generally lasts 9.4 +/- 5.4 days.
- mostly appears **concurrently** with COVID-19 infection (86%)
- Histology: **thrombosis** extensive complement deposition in endothelial cells
- viral symptom phase (TS), early inflammatory phase (TEI), or later,

Enanthem



Red Half-Moon Nail



-Transversal red bands first reported in patients with Kawasaki disease, localized in the nail isthmus.

-localized microvascular injury secondary to inflammatory immune response and procoagulant state

International Journal of Dermatology, First published: 29 August 2020, DOI: (10.1111/ijd.15167)

MIS-C



- systemic inflammation/vasculitis mimicking Kawasaki disease
- Rare, Black and Hispanic children are disproportionately affected
- Occurs 2-6 weeks after COVID infection (mild, asymptomatic), manifesting as hyperinflammatory response that occur when maximum level of antibodies
 - Almost all patients **tested positive**, suggesting that the development of **MIS-C was delayed by days or week**
 - resulted from delayed immunologic responses to infection by SARS-CoV-2
- Skin findings:
 - erythematous polymorphic (45-75%),
 - erythema and or firm induration of hands and feet (10-15%), oral mucositis (25-75%) conjunctivitis (30-80%)
- Over 90% experienced symptoms involving at least 4 organ systems and 58% needed treatments in ICU.
 - Predominant GI, mucocutaneous, and cardiovascular complications
 - Those under 5 have lowest risk of serious complications vs 10 years or older higher risk of severe disease, hypotension, shock and myocarditis

Summary



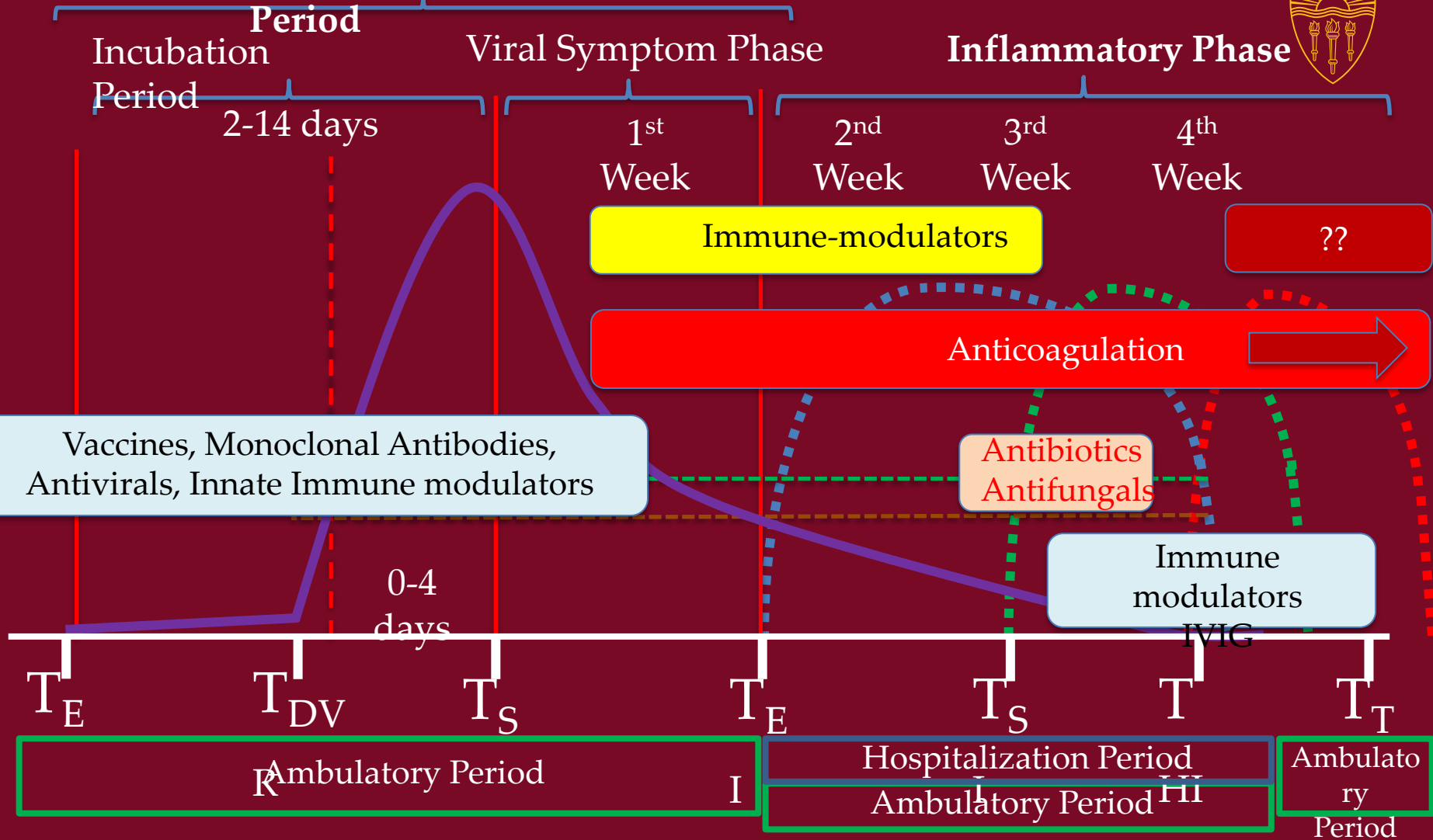
- Skin manifestations of COVID 19 nonspecific and heterogeneous
- Appear at different times in disease, with different duration, severity and prognosis
- Important not to overcall COVID 19 related eruptions and overlook other diagnosis
- Pseudo-chilblains appeared **later** in course of disease, lasted longer (12.7 days) and associated with **mild** disease, negative COVID test
- Livedoid reticularis/vasculitis seen in **older hospitalized** patients with **severe disease**



SARS-CoV-2 Vaccine Cutaneous Side Effects and Immunosuppressants



Viral Replication



Background – COVID-19 Vaccines



- Four main types of COVID-19 vaccines in use around the world:
 - messenger RNA–based vaccines
 - BNT162b2 (Pfizer-BioNTech, New York, New York) and mRNA-1273 (Moderna, Inc., Cambridge, Massachusetts)
 - adenoviral vector vaccines
 - ChAdOx1 nCoV-19 (AstraZeneca-Oxford), Gam-COVID-Vac (Gamaleya National Centre of Epidemiology and Microbiology), Ad26.COV2.S (Janssen Pharmaceuticals, Inc), and Ad5-nCoV (CanSinoBIO)
 - Protein subunit vaccines
 - Novavax, Cuban vaccines
 - inactivated whole-virus vaccines
 - BBIBP-CorV (Sinofarm) and CoronaVac (Sinovac Life Sciences)

Background—Structure of SARS-Cov-2

- SARS-CoV-2 consists of four structural proteins:
 1. S-spike protein (outer spiky glycoprotein)—main target
 - 2. Envelope protein (E)
 - 3. Membrane glycoprotein (M)
 - 4. Nucleocapsid protein (N)
 - interfere with the host’s immune system, enhancing the attachment and transportation into the host cells.

Mechanism of Action of mRNA Vaccines



- mRNA is covered with lipid microvesicles (liposomes) which protect it from degradation and carry it into the human cells.
- mRNA is transferred to the ribosomes, spike protein is translated and exposed on the surface of the host cells
 - spike protein molecules stimulate adaptive immune responses
- PEG (Polyethylene glycol) stabilizes liposomal capsule, can cause allergic reactions and anaphylaxis

Mechanism of Action of mRNA Vaccines



- Vaccine signaling via innate immune system
 - **adjuvant** that activates the innate immune system via TLR3 and TLR-7 and provides the necessary second signal
- Both ssRNA and dsRNA) activate the inflammasome in the cytosol.
- Trigger an inflammatory response and generates **type I interferons**, known to flare autoimmune disease.
 - modifications to reduce interferon activation and reduce this risk
 - addition of stabilizing adjuvants and removal of interferon-stimulating double-stranded mRNA from final preparations.

Talotta R. Do COVID-19 RNA-based vaccines put at risk of immune-mediated diseases? In 371 reply to "potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a 372 possible link to an increase in autoimmune diseases". Clin Immunol. 2021;224:108665

Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. Nat 368 Rev Drug Discov. 2018;17(4):261-279. doi:10.1038/nrd.2017.243 369 370 13

Teijaro JR, Farber DL. COVID-19 vaccines: modes of immune activation and future challenges. Nat Rev Immunol. 2021;21(4):195-197.

Cutaneous Side Effects of Vaccines



- Variety of cutaneous adverse events have been reported
 - most are **injection-site reactions**, mild to moderate
 - Some rare **delayed inflammatory reactions** such as “COVID arm”
 - reactions to hyaluronic acid (**HA**) **dermal fillers**
- Some rare serious adverse events,
 - vaccine-induced prothrombotic immune thrombocytopenia
 - Anaphylaxis

Johnston MS, Galan A, Watsky KL, Little LJ. Delayed localized hypersensitivity reactions to the Moderna COVID-19 Vaccine. A Case Series JAMA Dermatology 2021;157(6):716-20

Injection Site Reactions

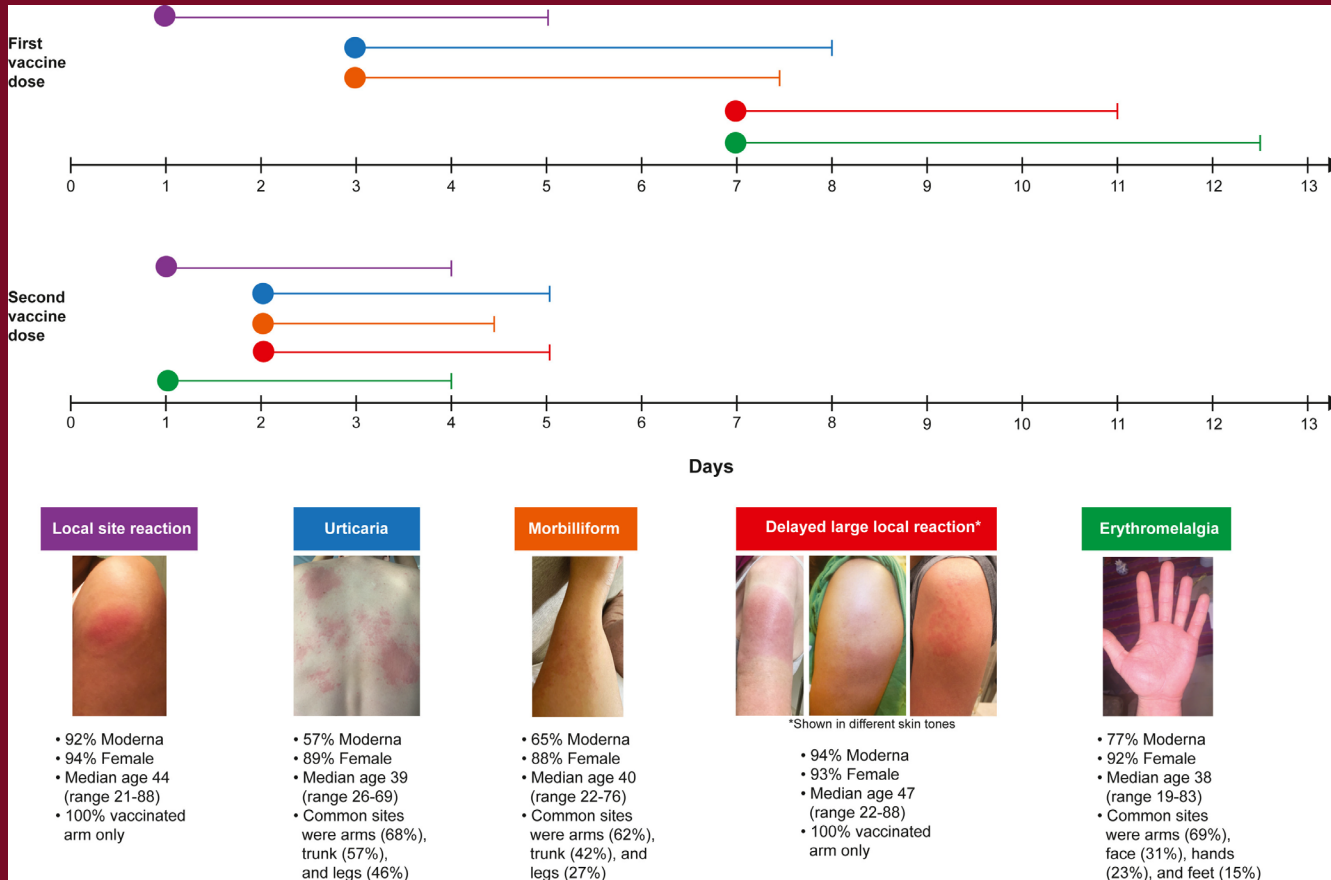


- **immediate injection-site reactions**, observed in 84.2% of the participants after the first dose.
- **delayed injection-site reactions** (an onset on or after day 8) occurred after the first dose (majority) and after the second dose.
- These reactions included erythema, induration, and tenderness.
- reactions typically resolved over the following 4 to 5 days.
- no safety concerns aside from transient local and systemic reactions

Johnston MS, Galan A, Watsky KL, Little LJ. Delayed localized hypersensitivity reactions to the Moderna COVID-19 Vaccine. A Case Series JAMA Dermatology 2021;157(6):716-20

.Baden LR, El Sahly HM, Essink B, et al; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384(5):403-416.

mRNA Vaccine Cutaneous Reactions



--most common morphologies were delayed large local reactions, local injection site reactions, urticaria, and morbilliform eruptions

McMahon D.E., Amerson E., Rosenbach M., Lipoff J.B., Moustafa D., Tyagi A., Desai S.R., (...), Freeman E.E. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases (2021) *Journal of the American Academy of Dermatology*, 85 (1), pp. 46-55.

Journal of the American Academy of Dermatology 2021 8546-55DOI: (10.1016/j.jaad.2021.03.092)

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Delayed Cutaneous Reactions to mRNA-1273 Vaccine.



<p>Dose 1</p> <p>Patient 1</p>	<p>Dose 2</p> <p>No recurrence</p>	<p>Dose 1</p> <p>Patient 2</p>	<p>Dose 2</p>	<p>Dose 1</p> <p>Patient 3</p>	<p>Dose 2</p>	<p>Dose 1</p> <p>Patient 4</p>	<p>Dose 2</p>
<p>Patient 5</p>	<p>No recurrence of palmar rash</p>	<p>Patient 6</p>		<p>Patient 7</p>		<p>Patient 8</p>	<p>No recurrence</p>
<p>Patient 9</p>		<p>Patient 10</p>		<p>Patient 11</p>		<p>Patient 12</p>	<p>No recurrence</p>

mRNA Vaccine Cutaneous Reactions



	Number patients with reactions after both doses	% Moderna	% Larger reaction with second dose	Onset of reaction in days after first vaccine Median (IQR)	Onset of reaction in days after second vaccine Median (IQR)	Representative First Dose Photo	Representative Second Dose Photo
Local site injection reaction	21	95%	45%	1 (0-1)	1 (0-1)	Day 1*	Day 2*
Delayed large local reaction	11	100%	27%	7.5 (7-8)	2 (1-3)	Day 8	Day 2
						Day 7	Day 1
Urticaria	4	75%	75%	2 (1-3)	0 (0-2)	Day 2	Day 2

--Less than 50% of patients with cutaneous reactions after the first dose experienced second-dose recurrence.

No reports of serious adverse events

--cutaneous reactions to COVID-19 vaccination are generally minor and self-limited, and should not discourage vaccination

Delayed HA Fillers Reactions



- Rare, occurs 24-48 hours post mRNA vaccine
- Mainly seen with HA fillers
- Rx: steroids, hyaluronidase, antihistamines, ACE inhibitors
- Not a contraindication to getting fillers





COVID-19 vaccine safety and efficacy in Immune-Mediated Inflammatory Disease

- Patients with Immune-Mediated Inflammatory Disease (IMID) may
 - experience disease flares
 - have diminished immune responses after COVID-19 vaccination, particularly B cell-depleting therapies.
- Two main concerns regarding vaccination against COVID-19 in patients with IMID:
 - the potential that biologics will reduce efficacy of the immune response
 - that vaccination may cause a flare of the underlying inflammatory disease.
- patients receiving biologics for treatment of inflammatory and autoimmune disease data from case series and observational studies
 - can safely receive mRNA vaccines
 - able to mount a detectable immune response with a few notable exceptions.

Impact of biologic therapy on response to COVID 19 vaccines –B-cell depleting



- most significant reduction in immune response to the COVID-19 vaccines with B cell depleting therapies (BCDT)
 - most prominent effect on anti-spike protein IgG and neutralization titers in the 6 months after dosing
- Studies are mixed
 - some studies suggest patients with even weakly reconstituted B cells had more robust vaccine responses, suggesting importance of timing vaccines with an interval between rituximab dosing and immunization.
 - Other studies patients failed to mount any detectable antibody response, even with a 6 month interval between rituximab dosing and vaccination.

Spiera R, Jinich S, Jannat-Khah D. Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS-CoV-2 vaccination in patients with rheumatic diseases. *Ann Rheum Dis.* 2021 Oct;80(10):1357-1359.

Biologic therapy on response to COVID 19 vaccines



- TNF-inhibitors
 - less substantial impact on immune response than BCDT, less robust immune responses compared to healthy controls.
 - BUT patients receiving TNF-I were found to have similar antibody titers, but a reduction in neutralization activity, as compared to healthy in COVaRiPAD study
- IL-17-inhibitors
 - Available case reports suggest that these patients produce a detectable antibody response.
- IL-12/23-inhibitors
 - No meaningful inhibition of immune response to COVID-19 vaccines.
 - Results from Deepak et al. found that IL-12/23-inhibitor use has a minimal impact on antibody titers compared to control and to other classes of biologics.

Society Recommendations Regarding Vaccination



- National Psoriasis Foundation
 - All patients with psoriasis should accept a vaccine as soon as it becomes available to them.
 - Psoriasis and/or psoriatic arthritis are not contraindications to vaccination.
- National Eczema Foundation
 - Atopic dermatitis is not a contraindication to vaccination. © Any patients with history of anaphylaxis or reaction to a vaccine ingredient should consult with their allergist prior to vaccination

National Psoriasis Foundation COVID-19 Task Force: Schedule of Updates to Guidelines. 477 National Psoriasis Foundation. https://npf-website.cdn.prismic.io/npf-website/75b7e5ef47837da-4196-9377-d83eda0bee92_TF+Schedule+of+Guidance+Stmt+Updates+121820.pdf. 479 Published October 16, 2020. Updated December 12, 2020. Accessed April 3, 2021.

BNT162b2 Vaccine induced Anaphylaxis



- Prospective cohort study in Israel (December 27, 2020 to Feb 22, 2021), 8102 patients with allergies, 429 (5%) classified as highly allergic and receive immunization under close medical supervision
 - High risk 1) prior anaphylactic reaction to any drug or vaccine 2) multiple drug allergies 3) multiple allergies 4) mast cell disorders
 - 2 hours of close observation by a dedicated allergy team after vaccination
- Results: 98% of the highly allergic individuals have no reaction, 6(1%) had mild allergic responses, and 3 (0.7%) had anaphylactic reactions
- High risk allergic patients can be safely immunized by using an algorithm under close supervision
- Shavit R, Maoz-Segal R, Iancovici-Kidon M, et al. Prevalence of Allergic Reactions After Pfizer-BioNTech COVID-19 Vaccination Among Adults With High Allergy Risk. *JAMA Netw Open*. 2021;4(8):e2122255. doi:10.1001

Psoriasis



- Psoriasis doesn't increase risk of COVID but comorbidities are strong risk factors for poor outcome
- Biologics do not increase COVID19 risk or hospitalization mortality
- Rare 60 VAERS reports of psoriasis flares with COVID-19 vaccine, no differences with other vaccines
- COVID-19 infection can cause flares of psoriasis, even with mild COVID-19 infection
- Gelfand JM, Armstrong A et al National Psoriasis Foundation COVID-19 Task Force guidance for management of psoriatic disease during the pandemic: Version 2-Advances in psoriatic disease management, COVID-19 vaccines, and COVID-19 treatments. J Am Acad Dermatol. 2021 May;84(5):1254-1268

International Pemphigus and Pemphigoid Foundation



- Patients with autoimmune bullous diseases should be vaccinated when a vaccine is available to them, as these patients are also at high risk for complications of COVID-19.
- In most cases, immunosuppressive treatment should not be interrupted to receive a vaccine as this could result in relapse or flare of disease.
- In patients treated with rituximab, vaccination should be completed 2 weeks prior to the start of rituximab treatment whenever possible, otherwise it is best to wait 4-6 months after the last rituximab infusion.

COVID-19 Monoclonal Antibodies



- Clearly indicated in Immune-Mediated Inflammatory Disease (IMID) and in Immunosuppressed Patients
- Monoclonal Antibodies quickly lose potency against rapidly emerging SARS-Cov-2 variants
- Bebtilovimab still considered effective
 - Non-hospitalized ≥ 18 or older mild to moderate
 - Within 7 days of symptom onset
 - Alternative when both Paxlovid and remdesivir not available, feasible to use

NIH COVID-19 Treatment Guidelines on Anti-SARS-CoV-2 Monoclonal Antibodies Accessed 08/26/2022

Antivirals



- Marked reduction of death (80%) and hospitalization (75%) in 65 + with nirmatrelvir and ritonavir (Paxlovid) use during Omicron surge
- early use of antivirals associated with reduction of death Paxlovid (66%) and molnupiravir (50%) among hospitalized patients without need for oxygen supplementation
- Early use of antivirals important for 65+ and for those immunocompromised

Arbel R et al Nirmatrelvir Use and Severe COVID-19 Outcomes During the Omicron Surge NEJM
Wong CK et al Lancet Infectious Diseases

Summary on COVID vaccines and IMID



- All patients with IMID should be immunized
- Neither IMID nor concurrent biologic use are contraindications to vaccination.
- Patients receiving biologics, and particularly those on BCDT, may produce diminished immune responses
 - BCDT > ABA, JAK, MTX
- patients receiving immunomodulating therapies will require alternative regimens (booster, combination vaccines, long acting monoclonal) to achieve a adequate response
 - Long acting tixagevimab/cligavimab (Evusheld) pre-exposure prophylaxis
 - adults and adolescents aged 12 and older with moderate to severe immune compromise due to medical condition or immunosuppressants or contraindications to the current vaccine
- Important to continue to follow patients with IMID after vaccination to determine vaccine safety, efficacy, and duration especially with new emerging variants

Summary



- Delayed hypersensitivity reaction (localized injection site reactions)
 - self-limited and not associated with serious adverse effects of vaccine
 - not a contraindication to subsequent vaccination
- COVID vaccines are safe in patients with IMID on biologics
 - B-cell depleting therapy require special attention to timing of vaccine dose
 - JAK, MTX, abatacept
- Booster dose is now recommended for all immunosuppressed patients in light of emerging variants
- Bebtilovimab monoclonal antibody treatment is still effective to prevent the newest variants



Thank You!
Questions???
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